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EXAMINER	
BRUSCA, JOHN S	
ART UNIT	PAPER NUMBER
1631	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/600,935	MANSURIPUR ET AL.	
	Examiner	Art Unit	
	John S. Brusca	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-80* is/are pending in the application.

4a) Of the above claim(s) *5,28,40-63 and 72-80* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-27,29-39 and 64-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1-80 are pending.

Claims 5, 28, 40-63, and 72-80 are withdrawn

Claims 1-4, 6-27, 29-39, and 64-71 are rejected.

Claim Rejections - 35 USC § 112

2. The rejection of claims 23 and 24 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention in the Office action mailed 03 June 2008 is withdrawn in view of the amendment filed 07 October 2008.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 30-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims recite a storage device comprising a coherent sequence of binary data. The specification at the time of filing does not describe "coherent" sequences.

5. Claims 1-4, 6-27, 29, 33, 35-37, 39, and 64-71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In In re Wands (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation." These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to practice the claimed invention one of skill in the art must transport individual molecules of DNA to desired locations, add desired nucleotide sequences or other spatially define markers to the molecule, and determine the sequence of an individual DNA molecule as part of a process of storing and reading data. For the reasons discussed below, there would be an unpredictable amount of experimentation required to make and use the claimed invention.

b) The specification presents guidance to utilize microfluidic devices and electrophoretic devices to move DNA molecules without providing guidance to be able to determine where an individual molecule is with the precision required to execute memory write and read operations on an individual molecule. The specification does not provide specific guidance regarding how data is to be processed for encoding into the sequences of DNA molecules, nor does the specification provide guidance regarding how DNA sequences of individual molecules are to be processed to regenerate stored data. The specification provides guidance to synthesize individual

molecules to comprise a desired sequence on pages 19-33, and to use single bases or pairs of bases to encode binary data on page 10 and figures 8A and 8B. Write mechanism 1 requires in situ chemical synthesis. In situ synthesis is a time consuming and complicated procedure and the specification does not show how such a procedure is compatible with a read-write memory storage apparatus that functions with a practical time period. Write mechanism 2 requires that individual nucleotides are added to a chamber containing the growing chain and a polymerase, but the specification does not address how to prevent errors due to inlet of more than one nucleotide, or how a polymerase incorporates a single substrate molecule with perfect efficiency even though enzymes generally require minimum concentrations of substrates to function. Write mechanisms 3-5 require modification of individual DNA molecules or other polymers at precise positions, but the specification does not provide specific guidance for locating modifications at precise positions in an individual molecule. Read mechanisms 1 and 2 require use of a nanopore or atomic force microscopy without providing specific guidance as to the nanopore or the parameters that can be measured to sequence through a nanopore or atomic force device. the specification provides guidance to use optical tweezers to move individual molecules form one part of the apparatus to another.

c) The specification does not provide working examples of any embodiment of the claimed invention.

d) The nature of the invention, synthesis of sequences or markings on individual molecules and subsequent determination of sequence or other features on individual molecules, is complex.

e) Rhee et al., published 4 years after the effective filing date of the instant application, shows that nanopore sequencing is a promising idea that has not yet been reduced to practice. Among the practical problems to nanopore sequencing that Rhee et al. notes are that alpha-hemolysin pores and other nanopores used allow for discrimination of some sized of single stranded DNA, but do not allow for sequencing. McCauley et al. reviews the use of optical tweezers to manipulate DNA. McCauley et al. shows in figure 1 that optical tweezers have been used to stretch DNA molecules to which beads have been attached to measure physical parameters of DNA molecules. McCauley et al. further details experiments using DNA bound to protein molecules that are manipulated by optical tweezers. McCauley et al. does not show use of optical tweezers to transport DNA within a device.

f) The skill of those in the art of molecular biology is high.

g) Because the claimed subject matter is drawn to aspects of manipulation of individual molecules that are not shown in the prior art, the predictability of the claimed subject matter is poor.

h) The claims are broad in that they encompass subject matter not detailed sufficiently in the specification or the prior art to avoid undue experimentation.

The skilled practitioner would first turn to the specification for guidance in practicing the claimed subject matter, however the specification does not provide working examples or sufficiently detailed guidance to manipulate individual molecules as required by the claimed subject matter. As such, the skilled practitioner would turn to the prior art for the guidance that is missing from the specification. However the prior art does not show methods of manipulation of individual molecules as in the claimed subject matter. Finally said practitioner would turn to trial

and error experimentation to practice the claimed subject matter. Such represents undue experimentation.

6. Applicant's arguments filed 07 October 2008 have been fully considered but they are not persuasive.

The applicants state that the Office has misconstrued the claimed subject matter, but the applicants do not point to limitations of the claimed subject matter that are inconsistent with the description of the claimed subject matter in the rejection detailed above. The applicants state that In re Wands dealt with cells rather than the claimed subject matter, however the Wands factors are used for assessment of enablement for all categories of claimed subject matter, see MPEP 2164.01(a). The applicants state that although the in situ synthesis of write mechanism 1 is slow, the amount of time required to use the claimed device is irrelevant, however it is relevant to consider the degree of difficulty and amount of experimentation required as a factor when assessing whether using the claimed device would require undue experimentation. Write mechanism 2 allows for errors. The applicants argue that error correction of such errors is taught in the specification, however the specification does not describe what level of errors would be present if write mechanism 2 were used, or if the level of errors present would make error correction mechanisms impractical. The specification does not provide a working example to assess the practicality of the prophetic write mechanism 2. The applicants state without evidence that a tether would allow an enzyme to function at low base concentration. Since the specification does not show that write mechanism 2 is a practical method because the specification lacks any working examples, the applicants arguments are not persuasive in the absence of evidence that the prophetic mechanisms described in the specification are practical.

The concerns discussed in the above rejection are based on well known requirements for enzymes to require a minimal concentration of substrates before the enzymes can catalyze their specific reaction. The applicants state without evidence that write mechanisms 3-5 could operate by manipulation and positioning of individual molecules at precise positions. The guidance given in the specification to perform such manipulation is to use optical tweezers, however it is not apparent from the specification or the prior art (see McCauley et all noted in the above rejection) how optical tweezers could be used to manipulate individual molecules to particular locations. Such manipulation is required to use the claimed devices. Regarding the ability of nanopores to determine the sequence of a polynucleotide, the applicants agree that Rhee et al. (noted in the above rejection) shows that single base discrimination is not possible with alpha hemolysin nanopores. The applicants state that multiple bases may be used but do not point to guidance in the specification to use more than 2 bases per datum, and do not show provide evidence that alpha hemolysin nanopores can resolve two base units. The applicants state that the specification provides guidance to make nanotubes using argon ions, but no detailed guidance or working examples of such nanopores are in the specification, and Rhee et al., published after the instant effective filing date, mentions use of synthetic nanopores for polynucleotide sequencing, but does not show success in sequencing polynucleotides using synthetic nanopores, or use of synthetic nanopores prior to the instant effective filing date. The applicants provide Exhibits A-F which are addressed in turn below:

Exhibit A (Mansuripur) does not disclose the claimed devices in sufficient detail to enable the claimed devices.

Exhibit B (Thorsen et al.) is not prior art and therefore cannot serve to supplement what is missing in the instant specification to enable the claimed devices. Exhibit B does not disclose the claimed devices, and instead uses dye colored fluids in a microfluidic device to store data.

Exhibit C (Mansuripur et al.) is not prior art and therefore cannot serve to supplement what is missing in the instant specification to enable the claimed devices. Exhibit C shows on page 235 that 20 base sequences are not resolvable in their system. Exhibit C does not show reduction to practice of the claimed devices.

Exhibit D (Skinner et al.) is not prior art and therefore cannot serve to supplement what is missing in the instant specification to enable the claimed devices. Exhibit D uses a studded polynucleotide read mechanism in figure 3 that is not described in the instant specification.

Exhibits E and F (Mansuripur et al. and Khulbe et al.) appear to be identical. Exhibits E and F are not prior art and therefore cannot serve to supplement what is missing in the instant specification to enable the claimed devices. Exhibit F shows a read mechanism in figure 4 in which a polynucleotide consisting of 50 A's and 100 C's is resolved by a nanopore. The specification does not describe a read mechanism in which each datum is 50-100 bases long.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 30-32, 34, and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Lagally et al.

The claims are drawn to a microfluidic device that moves molecular material encoding binary data to different locations within the device. In some embodiments the device comprises pumps and valves. In some embodiments the device comprises an electrophoresis device.

Lagally et al. shows in figure 1 a microfluidic device that comprises valves, pumps, and a capillary electrophoresis device. The device is used to amplify DNA by in situ PCR, followed by analysis of the DNA products by capillary electrophoresis within the device. Representative results of the analysis of the DNA produced in the reactions is shown in figure 2. Lagally et al. provides on pages 567-568 details of how the microfluidic device operates, including discussion of moving the DNA samples by pumping and use of valves. Regarding the limitation that the molecular material encoded binary data, the limitation is inherent in any DNA sequence of bases and does not provide a structural limitation that distinguishes from any base sequence in a polynucleotide.

9. Applicant's arguments filed 07 October 2008 have been fully considered but they are not persuasive. The applicants state that Legally et al. does not show DNA encoded with binary data. The limitation in claim 30 that the molecular material is encode with binary data is an inherent property of any sequence of nucleotides in a polynucleotide and the rejection is maintained.

Conclusion

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca whose telephone number is 571 272-0714. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie A. Moran can be reached on 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/John S. Brusca/
Primary Examiner
Art Unit 1631

jsb